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Staging classification for cancer of the ovary, fallopian tube, and peritoneum☆

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Introduction

Ovarian cancer is the seventh most common cancer diagnosis among women worldwide, and the fifth most common cancer diagnosis among women in higher-resource regions [1]. The world rate is estimated to be 6.3 per 100 000 women, and is highest in high-resource countries (9.3 per 100 000 women) [1]. Primary peritoneal cancer and primary fallopian tube cancer are rare malignancies but share many similarities with ovarian cancer. Clinically, these 3 cancers are managed in a similar manner [2].

The main purpose of staging systems is 2-fold: to provide standard terminology that allows comparison of patients between centers; and to assign patients and their tumors to prognostic groups requiring specific treatments. Ovarian cancer is staged surgically and pathologically, and the last revision of the FIGO staging classification was made in 1988 (Rio de Janeiro). The FIGO Committee on Gynecologic Oncology feels that it is time to revise this classification to improve utility and reproducibility. Cancer staging evolves continuously as scientific developments occur, diagnostic methods improve, and more accurate prognostic information becomes available. Over the past quarter of a century, several scientific developments have challenged traditional concepts in ovarian cancer. Initially, it was recognized that ovarian cancer is not a homogeneous disease, but rather a group of diseases—each with different morphology and biological behavior. Approximately 90% of ovarian cancers are carcinomas (malignant epithelial tumors) and, based on histopathology, immunohistochemistry, and molecular genetic analysis, at least 5 main types are currently distinguished: high-grade serous carcinoma (HGSC [70%]); endometrioid carcinoma (EC [10%]); clear-cell carcinoma (CCC [10%]); mucinous carcinoma (MC [3%]); and low-grade serous carcinoma (LGSC [<5%]) [3]. These tumor types (which account for 98% of ovarian carcinomas) can be reproducibly diagnosed by light microscopy and are inherently different diseases, as indicated by differences in epidemiologic and genetic risk factors; precursor lesions; patterns of spread; and molecular events during oncogenesis, response to chemotherapy, and prognosis [4,5]. Much less common are malignant germ cell tumors (dysgerminomas, yolk sac tumors, and immature teratomas [3% of ovarian cancers]) and potentially malignant sex cord-stromal tumors (1%–2%, mainly granulosa cell tumors). The biomarker expression profile within a given histotype is consistent across stages. Ovarian cancers differ primarily based on histologic type.

In the era of personalized cancer medicine, reproducible histopathologic diagnosis of tumor cell type is a sine qua non for successful treatment. Different tumor histotypes respond differently to chemotherapy. Even if different patterns of dissemination justify the use of separate staging systems for each type of ovarian carcinoma, such a complex classification would not be practical. For the sake of simplicity, the Committee chose a flexible staging system that takes into account the most relevant prognostic parameters shared by all tumor types. It was unanimously agreed that histologic type should be designated at staging (i.e. HGSC, EC, CCC, MC, and LGSC; other or cannot be classified; and malignant germ cell tumors and potentially malignant sex cord-stromal tumors).

Another discovery that influenced the new FIGO staging occurred in 2001, when patients with *BRCA* mutation (breast–ovarian cancer syndrome) undergoing risk-reducing salpingo-oophorectomy were found to have high-grade serous tubal intraepithelial carcinoma (STIC) not in the ovary but in the fallopian tube and, particularly, in the fimbria [6]. Although STIC is capable of metastasizing and, therefore, cannot be considered carcinoma in situ, compelling evidence for a tubal origin of *BRCA*-positive HGSC (approximately 60% of *BRCA* cases) has accumulated over the past decade [7,8]. High-grade STIC has also been encountered in an undetermined number of advanced-stage sporadic HGSCs associated with ovarian tumor masses and in rare cases of primary tubal or peritoneal HGSCs without obvious ovarian involvement. The relative proportion of HGSCs of ovarian and tubal derivation is unknown, mainly because tumor growth in advanced-stage cancers conceals the primary site. Even in cases involving *BRCA* mutation, evidence of a tubal origin of HGSCs is incomplete and a multicentric origin of these tumors (i.e. arising from ovarian surface mesothelial invaginations or inclusion cysts with subsequent müllerian neometaplasia, from implantation of tubal-type epithelium into the

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ovary [endosalpingiosis], or from the pelvic peritoneum [the so-called secondary müllerian system]) cannot be excluded.

As indicated above, HGSCs and LGSCs are fundamentally different tumor types and, consequently, different diseases. High-grade serous carcinomas are the most common ovarian carcinomas and most patients present with advanced-stage disease (approximately 80%); tumors confined to the ovary at diagnosis are distinctly uncommon (<10%). By contrast, LGSCs are much less common, usually contain a serous borderline component, and carry *KRAS* and *BRAF* mutations [9,10]. High-grade serous carcinomas are not associated with serous borderline tumors and typically exhibit *TP53* mutations and *BRCA* abnormalities resulting in chromosomal instability.

The putative tubal or peritoneal origin applies exclusively to HGSCs and not to the vast majority of ECs and CCCs, which are thought to arise in the ovary from endometriosis. However, because of the higher frequency of HGSCs and their apparent multicentric origin along müllerian-derived tissues, most Committee members felt that FIGO staging of ovarian, peritoneal, and fallopian tube cancers should be considered collectively. The primary site (i.e. ovary, fallopian tube, or peritoneum) should be designated where possible. In some cases, it might not be possible to delineate the primary site clearly; such cases should be listed as "undesignated."

Although a significant number of HGSCs might not arise from the ovary, and the term "ovarian cancer" would not be pathogenically precise in every case, ovarian involvement is the rule in almost all cases. In view of the rarity of HGSCs associated with tubal tumor masses, it is unlikely that all HGSCs originate in the fallopian tube. The term HGSC of ovary should be kept until the different origins of ovarian tumors are better understood. Terms such as "müllerian" or "pelvic serous carcinoma" are not recommended because they create confusion for patients, physicians, and medical investigators [11].

The process of the proposed changes to the staging of ovarian, fallopian tube, and primary peritoneal cancer started 3 years ago under the leadership of the Chair of the FIGO Committee on Gynecologic Oncology, Professor Lynette Denny. The proposal was sent to all relevant gynecologic oncology organizations and societies worldwide, such as the Gynecology Cancer Intergroup; the International Gynecologic Cancer Society; the European Organization for Research and Treatment of Cancer; the American Society of Gynecologic Oncology; the European Society of Gynecologic Oncology; the National Cancer Research Network, UK; the Australian Society of Gynaecological Oncology; the Korean Society of Gynecologic Oncology; and the Japanese Society of Obstetrics and Gynecology. Input was collated, evaluated, and formulated into the staging that is presented herein. The new staging was reached by consensus of those participating in the FIGO meeting held in Rome, Italy, on October 7, 2012, some of whom were representatives of their organizations. The new staging was presented to the FIGO Executive Board on October 12, 2012, and approved 2 weeks later. Subsequently, the proposal was presented to and approved by the American Joint Commission on Cancer and the International Union Against Cancer, the latter in May 2013. The following is the consensus agreement that resulted from these efforts and represents new criteria for staging of these gynecologic cancers.

Stage I: Tumor confined to ovaries or fallopian tube(s)

T1-N0-M0

IA: Tumor limited to 1 ovary (capsule intact) or fallopian tube; no tumor on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings

T1a-N0-M0

IB: Tumor limited to both ovaries (capsules intact) or fallopian tubes; no tumor on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings

T1b-N0-M0

IC: Tumor limited to 1 or both ovaries or fallopian tubes, with any of the following:

IC1: Surgical spill

T1c1-N0-M0

IC2: Capsule ruptured before surgery or tumor on ovarian or fallopian tube surface

T1c2-N0-M0

IC3: Malignant cells in the ascites or peritoneal washings

T1c3-N0-M0

Comment

Stage I ovarian or fallopian tube cancer is confined to the ovaries or the fallopian tubes and peritoneal fluid/washings. Tumor rupture or surface involvement by tumor cells warrants a stage of IC. It is not possible to have stage I peritoneal cancer.

Controversial issues

Bilateral involvement (stage IB). Independent contralateral primary tumor versus implants or metastases

Stage IB is relatively uncommon, occurring in only 1%–5% of stage I cases [12,13]. Occasionally, a large stage IB ovarian tumor is associated with a contralateral normal-size ovary exhibiting small and superficial foci of tumor, suggesting that the latter are metastatic. Among stage I tumors with bilateral involvement, one-third have this appearance [14].

What constitutes ovarian surface involvement? Excrescences? Microscopic involvement?

Surface involvement of the ovary or fallopian tube should be considered present only when tumor cells are exposed to the peritoneal cavity. It is characterized by exophytic papillary tumor on the surface of the ovary or fallopian tube or on the outer surface of a cystic neoplasm replacing these organs; rarely, a smooth ovarian tumor surface will be shown to have an exposed layer of neoplastic epithelium. Assessment of surface involvement requires careful gross examination.

Dense adhesions often cause rupture during surgery. Should these cases be considered stage II?

Limited evidence suggests that dense adhesions of an apparent stage I tumor requiring sharp dissection (or when dissection results in tumor rupture) result in outcomes equivalent to tumors in stage II [15,16]. At present, however, it is not clear whether upstaging based on dense adhesions is warranted. A recent study suggests that it is not [17].

Does histologic grade influence prognosis of stage I tumors?

In several series of stage I tumors, multivariate analyses identified degree of differentiation as the most powerful prognostic indicator of disease-free survival [15,18,19]. With the exception of ECs and MCs, the histologic grade is implicit in the tumor type (i.e. HGSC, LGSC, CCC [the vast majority are high-grade tumors]). Currently, grade 3 ECs are considered to be the same as HGSCs. Most MCs involving the ovary are metastatic from the gastrointestinal tract and some might appear well differentiated (G1).

Does rupture during surgery worsen prognosis in the absence of excrescences, ascites, or positive washings?

This is controversial. Whereas some studies found that intraoperative capsule rupture portends a higher risk of disease recurrence [19,20], others did not [14,15,18,21,22]. In a multivariable analysis, capsule rupture and positive cytologic washings remained independent predictors of worse disease-free survival [20]. Rupture should be avoided during primary surgery of malignant ovarian tumors confined to the ovaries. Data from several studies suggest that stage I CCC is more frequently stage IC compared with other cell types [17], possibly because of an increased risk of rupture [23].

Are positive washings worse than/the same as capsule rupture?

In multivariable analysis, capsule rupture and positive cytologic washings remained independent predictors of worse disease-free survival [20].

Recommendations

- Histologic type, which in most cases includes grade, should be recorded.
- All individual subsets of stage IC disease should be recorded.
- Dense adhesions **with histologically proven tumor cells** justify upgrading to stage II.
- If rupture is noted, peritoneal washing and cytology study are indicated.

Stage II: Tumor involves 1 or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or primary peritoneal cancer

T2-N0-M0

IIA: Extension and/or implants on uterus and/or fallopian tubes and/or ovaries

T2a-N0-M0

IIB: Extension to other pelvic intraperitoneal tissues

T2b-N0-M0

Comment

Stage II ovarian cancer is still difficult to define. It comprises a small and heterogeneous group making up less than 10% of ovarian cancers. It is defined as extension or metastasis to extraovarian/extratubal pelvic organs and may include curable tumors that have directly extended to adjacent organs but have not yet metastasized, as well as tumors that have seeded the pelvic peritoneum by metastasis and, therefore, have a poor prognosis. Of note, the sigmoid colon is within the pelvis, and therefore sigmoid involvement only is considered stage II. The Committee felt that subdividing this small category further into IIB1 and IIB2 (i.e. microscopic and macroscopic pelvic peritoneal metastases) was not based on evidence/biology. All stage II disease is treated with adjuvant chemotherapy, so subclassification is not essential. Also, the old substage IIC (i.e. IIA or IIB but with tumor on surface, capsule ruptured, or ascites or positive peritoneal washing) was considered redundant and eliminated.

Controversial issues

Is it biologically justified to separate the pelvic from the extrapelvic peritoneum? Is disease outside the ovary but below the pelvic brim so much better that it warrants a separate stage?

Biologically, this is stage III disease and it is only because of the anatomic location in the pelvis that it is designated stage II. Some investigators claim that the peritoneum is an anatomic unit and that pelvic involvement and extrapelvic involvement are prognostically similar. Thus, they suggest defining as stage III all cases with peritoneal involvement including uterine serosa (as is done for stage IIIA endometrial carcinoma of the uterus). Most Committee members felt that there was a clear division of stage II and III disease in terms of survival, and therefore the subdivision of IIA and IIB remains.

Recommendations

- To separate direct extension from metastases.
- To compare outcome of stage II and early stage III cases.

Stage III: Tumor involves 1 or both ovaries or fallopian tubes, or primary peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes

T1/T2-N1-M0

IIIA1: Positive retroperitoneal lymph nodes only (cytologically or histologically proven):

IIIA1(i) Metastasis up to 10 mm in greatest dimension
IIIA1(ii) Metastasis more than 10 mm in greatest dimension

IIIA2: Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes

T3a2-N0/N1-M0

IIIB: Macroscopic peritoneal metastasis beyond the pelvis up to 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes

T3b-N0/N1-M0

IIIC: Macroscopic peritoneal metastasis beyond the pelvis more than 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes (includes extension of tumor to capsule of liver and spleen without parenchymal involvement of either organ)

T3c-N0/N1-M0

Comment

Most ovarian cancers are HGSCs that usually present in stage III, with the vast majority (84%) stage IIIC [12]. These tumors characteristically spread along peritoneal surfaces involving both pelvic and abdominal peritoneum including the omentum, surfaces of the small and large bowel, mesentery, paracolic gutters, diaphragm, and peritoneal surfaces of the liver and spleen. A finding of ascites occurs in two-thirds of cases. Lymph node metastases are found in the majority of patients who undergo node sampling or dissection and in up to 78% of advanced-stage patients [24]. Approximately 9% of patients with tumors that otherwise appear to be stage I have lymph node metastases; the corresponding figures for stages II, III, and IV are 36%, 55%, and 88%, respectively [25]. Rarely, inguinal or supraclavicular (stage IV) node metastases will be the presenting manifestation of ovarian carcinoma [26].

Less than 10% of ovarian carcinomas extend beyond the pelvis with exclusively retroperitoneal lymph node involvement. Evidence in the literature indicates that these cases have a better prognosis than that of tumors with abdominal peritoneal involvement [27–32]. The new staging includes a revision of stage III patients and assignment to stage IIIA1 based on spread to the retroperitoneal lymph nodes without intraperitoneal dissemination. Stage IIIA1 is further subdivided

into IIIA1(i) (metastasis ≤10 mm in greatest dimension) and IIIA1(ii) (metastasis >10 mm in greatest dimension), even if there are no retrospective data supporting quantification of the size of metastasis in IIIA1. Involvement of retroperitoneal lymph nodes must be proven cytologically or histologically.

Controversial issues

Could some carcinomas that have extended beyond the pelvis with exclusively retroperitoneal lymph node involvement (stage IIIA1) represent independent LGSCs arising in retroperitoneal lymph nodes from endosalpingiosis?

Serous borderline tumors and LGSCs may develop in retroperitoneal and cervical lymph nodes from endosalpingiosis, often in association with serous borderline tumors of the ovary and with favorable prognosis [33,34]. In none of the reported case series was a histopathologic distinction made between HGSC and LGSC.

Should the new stage IIIA1 be limited to involvement of the retroperitoneal lymph nodes below the diaphragm?

It was suggested that upward nodal involvement (e.g. mediastinal nodes) should be included but, for now, the Committee felt that the stated limitation was appropriate.

Is the 2-cm cutoff between IIIB and IIIC justified?

Regarding the amount of peritoneal involvement, it was claimed that stage III tumors should be divided into microscopic and macroscopic, and if the latter measurement (in centimeters) should be given. Further distinction should be made between single small lesions within the omentum (<2 cm) and diffuse peritoneal disease including the upper abdomen and diaphragm.

Specific mention should be given to **bowel infiltration** (transmural with mucosal involvement) and **umbilical deposit** (currently IVB); however, some consider that involvement of the umbilicus should be IIIC rather than IV as it represents peritoneal extension into the urachal remnant. Similarly, isolated parenchymal liver metastasis and splenic parenchymal metastasis are susceptible to cytoreductive surgery and, according to some investigators, should be IIIC, although this was not adopted by the Committee (i.e. transmural bowel infiltration, umbilical deposit, and parenchymal metastases in the liver and spleen or elsewhere such as lung and bone are assigned to stage IVB).

Recommendations

- To classify IIIA1 cases histologically.
- To compare outcome of stage IIIA1(i) and IIIA1(ii) cases.
- To compare outcome of stage IIIA1 and IIIA2 cases.

Stage IV: Distant metastasis excluding peritoneal metastases

Stage IVA: Pleural effusion with positive cytology

Stage IVB: Parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

Any T, any N, M1

Comment

Stage IV is defined as distant metastasis and includes patients with parenchymal liver/splenic metastases and extra-abdominal metastases; 12%–21% of patients present with stage IV disease [12]. Extension of tumor from omentum to spleen or liver (stage IIIC) should be differentiated from isolated parenchymal metastases (stage IVB).

Controversial issues to be resolved in the future

Should macroscopic and positive lymph nodes above the renal vessels be considered stage III or IV?

Notes

- The primary site (i.e. ovary, fallopian tube, or peritoneum) should be designated where possible. In some cases, it might not be possible to delineate the primary site clearly; such cases should be listed as "undesignated."
- The histologic type should be recorded.
- The staging includes a revision of stage III patients; assignment to stage IIIA1 is based on spread to the retroperitoneal lymph nodes without intraperitoneal dissemination because an analysis of these patients indicates that their survival is significantly better than that of patients with intraperitoneal dissemination.
- Involvement of retroperitoneal lymph nodes must be proven cytologically or histologically.
- Extension of tumor from omentum to spleen or liver (stage IIIC) should be differentiated from isolated parenchymal metastases (stage IVB).

Recommendation for future consideration

- Splenectomy seems to take care of isolated metastases in a better way than partial hepatectomy. In future, isolated splenic metastasis may be considered stage IIIC rather than stage IV, whereas parenchymal liver metastasis would remain stage IVB.

Conflict of interest

L.D. and N.B. have received honoraria for appearing on various speaker forums about HPV vaccination and have received research support from GlaxoSmithKline and MSD/Merck for HPV-related research. The other Committee members have no conflicts of interest.

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